Autonomic modulation of repolarization instability in patients with heart failure prone to ventricular tachycardia

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Submitted 3 June 2013; accepted in final form 6 August 2013

Ventricular tachyarrhythmias (VTs) related to structural heart disease are the most common cause of sudden cardiac death (SCD) in the Western world (7). Many of these occur in patients with ventricular scarring, related predominantly to coronary artery disease or dilated cardiomyopathies. Such scarring produces nonhomogenous myocyte loss, diminished myocyte coupling, ion channel dysfunction, and thus spatial heterogeneity in ventricular action potential repolarization and a prolonged corrected QT interval that predispose to ventricular arrhythmias and SCD (6, 12, 13, 18, 28, 48). Superimposed on this spatial heterogeneity, temporal (beat-to-beat) variation in cardiac repolarization across the ventricle has been recognized and shown to be elevated in ischemia and heart failure (HF) (10, 26, 35, 40). Increased QT variability (QTV) on the surface ECG, which is arguably a marker for compound spatiotemporal heterogeneity in repolarization, was found to predict appropriate device therapies in the Multicenter Automatic Defibrillator Implantation Trial II study as well as total and arrhythmic deaths in HF patients without defibrillators (24, 41, 50).

Common mechanisms influencing QTV include heart rate (HR) variability (HRV), autonomic changes, and the repolarization reserve itself, which is commonly seen in structural heart disorders (4, 5), may be the principle driver of elevated QTV in HF as well as its role in arrhythmogenesis are poorly understood. There is evidence suggesting that enhanced beat-to-beat fluctuations in repolarization duration in HF do not reflect merely incidental changes in HR and electrical restitution (10, 35, 40). As interventions that increase sympathetic stimulation shorten ventricular repolarization duration, increase spatial dispersion in repolarization, and increase QTV in normal hearts (1, 55), the elevated QT interval variability seen in HF patients may result from enhanced sympathetic drive and the subsequent diminution in the repolarization reserve (47, 52). On the other hand, the primary reduction in the repolarization reserve itself, which is commonly seen in structural heart disorders (4, 5), may be the principle driver of elevated QTV in these patients (31). Given the contrasting differences in the overall milieu in subjects with normal and myopathic hearts, it is imperative to understand the central mechanisms underlying elevated QTV in HF patients. In this study, we will therefore examine the effect of arrhythmogenic substrate on QTV in HF subjects and whether it can be modulated by autonomic control.

METHODS

Patient Population

The study population included 29 patients: 10 patients with ischemic or dilated cardiomyopathy undergoing clinically indicated VT ablation [HFVT(+)] group], 10 patients with ischemic or dilated cardiomyopathy undergoing clinically indicated implantable cardioverter defibrillator (ICD) implantation as per primary prevention guidelines (20) [HFVT(−) group], and 9 subjects with structurally normal hearts undergoing electrophysiological study (EPS) and catheter ablation for supraventricular tachycardia (Hnorm group). Patients with ischemic cardiomyopathy had undergone a recent noninvasive evaluation or coronary angiography to exclude active ischemia. All baseline medications were continued at the time of study. Patients of <18 yr of age or with permanent atrial fibrillation, sinus node disease (resting HR < 40 beats/min), ventricular preexcitation, heart block, permanent atrial or ventricular pacing, idiopathic VT, uncontrolled HF, an acute coronary event within the preceding 1 mo, and asthma

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were excluded. All patients provided informed consent. This study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide.

**ECG Recording**

A body surface 12-lead ECG was recorded before the intended procedure for 8 min under resting conditions at a sampling frequency of 1,000 Hz with the Bard electrophysiology system (LabSystem PRO version 2.4a EP, Bard, Lowell, MA). Patients rested for at least 30 min before the actual recording started. All procedures were formed under light conscious sedation with intravenous midazolam (1–2 mg) and fentanyl (25–50 μg) with continuous hemodynamic monitoring.

**Patients undergoing VT ablation.** All patients in the HFVT(+) group had a previously implanted ICD and experienced frequent ICD therapies for recurrent VT (cycle length: 351 ± 116 ms). None of these patients had previously undergone catheter ablation. None of the patients had VT storm or incessant VT. All patients were in stable sinus rhythm during study interventions. Catheters were positioned at the right ventricular apex and in the coronary sinus through a femoral vein. Atrial pacing was performed at two cycle lengths, 80 and 100 beats/min (MicroPace EPS 320 Cardiac Stimulator, Santa Anna, CA), each for 8 min. If the intrinsic rate was fast, maximum pacing rate was allowed up to 90 and 110 beats/min, respectively. Pharmacological interventions were then individually commenced through a peripheral vein: esmolol (a selective β₁-receptor blocker, 0.05–0.3 mg/kg⁻¹·min⁻¹) followed by isoprenaline infusion (1–3 μg/min) and atropine infusion (0.04 mg/kg single dose). This sequence of drug administration was followed in all subjects, in accordance with the rapid elimination pharmacokinetics of esmolol and isoprenaline compared with atropine (14a). The ECG during each intervention was recorded continuously for 8 min (49a). The infusions of esmolol and isoprenaline were rapidly up titrated to achieve their respective maximal dose within the first 3 min, which then continued until the end of each recording. A compulsory time gap of at least 5 min was allowed for drug washout after each intervention with the end point as the return of HR to the baseline level. Programmed ventricular stimulation was subsequently performed to assess the inducibility of VT. The procedure for VT mapping and ablation was performed as per the institutional protocol after completion of all study interventions.

**Patients undergoing ICD implantation.** The experimental protocol in the HFVT(−) group was similar to that applied to the HFVT(+) group. However, atrial pacing was performed through the pacing lead of the ICD, temporarily positioned in the right atrium, using a compatible pacing system. Pharmacological interventions were performed after ICD implantation. Programmed ventricular stimulation was then performed through noninvasive ECG to assess the inducibility of VT.

**Patients undergoing EPS.** Catheters were positioned through a femoral vein in the coronary sinus and right ventricle. The experimental protocol was similar to that of the HFVT(+) and HFVT(−) groups. However, pharmacological interventions were performed post EPS and catheter ablation for supraventricular tachycardia.

**QT Interval Variability Analysis**

The recorded ECG data were stored on removable media for semiautomated offline analysis. To measure QT intervals, usually lead I was chosen. If the signal in lead I was contaminated with noise, then an alternative lead with tall T waves was chosen. The algorithm proposed by Berger et al. (10) was used to measure beat-to-beat QT intervals. The operator defines a template QT interval on the chosen ECG channel by selecting the beginning of the QRS complex and the end of the T wave for one beat. The algorithm then finds the QT interval of all other beats by determining how much each T wave must be stretched or compressed in time to match the template closest. As this method takes into account the whole T wave, it is less susceptible to the measurement noise associated with conventional beat-to-beat delineation of the end of the T wave (9). To account for slow adaptation of the QT interval to the HR and intervention (56), only the last 3-min epochs of each 8-min recording were used for further analysis. The presence of atrial or ventricular ectopy and pacing was permitted unless such beats represented >5% of all beats over the 3-min period. Ventricular ectopic beats were detected automatically based on ECG QRS morphology and were excluded from analysis.

The QT response was calculated as the mean QT, and QTV was quantified as the SD of beat-to-beat QT intervals (SDQT) at baseline (3 min) and during the last 3 min of the study interventions (27, 49). Heart period mean and HRV [SD of RR intervals (SDRR)] were computed from the sequence of RR intervals. QT relative to HRV (QTV-to-HRV ratio) was computed as the ratio of SDQT to SDRR (27). Rather than separating QTV from HRV, this metric can be regarded as a composite measure of HR and QTV.

**Statistical Analysis**

Baseline demographic variables are presented as means ± SD for continuous data and counts for the categorical data. Comparisons between the HFVT(+) and HFVT(−) groups were carried out using one-way ANOVA with multiple Bonferroni post hoc comparisons or by χ² test (or Fisher’s exact test) as applicable.

To test for differences in electrocardiographic parameters between the three groups at baseline, one-way ANOVA was used. To test for differences in changes in ECG measurements from baseline to pacing or pharmacological intervention between groups, linear mixed-effects models were used. Within these models, intervention (i.e., basal/atrial pacing at 80 beats/min/atrial pacing at 100 beats/min or basal/esmolol/isoprenaline/atropine) and group [HFVT(+), HFVT(−), and HNorm] were included as fixed effects, and the patient identifier was included as a random effect to account for dependence within a patient. Initially, an interaction term between intervention and group was included in the linear mixed-effects models. Since this interaction term was not significant in every case, the final models contained only main effects, for which means and post hoc contrasts are reported. Results are presented as means ± SE.

The statistical software used was SAS 9.3 (SAS Institute, Cary, NC). Two-sided P values of <0.05 were considered statistically significant.

**RESULTS**

**Patient Characteristics**

The demographic characteristics of the patient groups are shown in Table 1. Other than VT inducibility, the baseline features in the HFVT(+) group were closely matched with the HFVT(−) group. The majority of patients in the HF groups (19 of 20 patients) were on a long-term stable dose of an oral β-blocker before the investigation. The HNorm group patients were younger and predominantly women, and most patients (6 of 9 patients) were not taking any medications.

The effects of pacing and pharmacological interventions on electrocardiographic parameters in the three groups of patients are shown in Table 2 and are further shown with respective mean plots in Figs. 1 and 2.

**HR Responses**

The basal heart period mean was longer in the HFVT(+) group compared with the HNorm group (P = 0.01). Compared with the basal state, the heart period mean increased marginally with esmolol (P = 0.09) and shortened significantly after isoprenaline (P = 0.02) and with atropine (P < 0.001) in all three groups. The relative baseline difference between HFVT(+) and
Table 1. *Patient characteristics*

<table>
<thead>
<tr>
<th></th>
<th>HFVT(+) Group</th>
<th>HFVT(−) Group</th>
<th>HNorm Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>63 ± 12</td>
<td>54 ± 13</td>
<td>36 ± 19</td>
<td>0.004*</td>
</tr>
<tr>
<td>Men/women, n</td>
<td>9/1</td>
<td>10</td>
<td>28</td>
<td>0.002†</td>
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<tr>
<td>Cardiomyopathy, n</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ischemic</td>
<td>8</td>
<td>8</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Nonischemic</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>30 ± 10</td>
<td>29 ± 8</td>
<td>63 ± 3</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2</td>
<td>4</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to first infarction, yr</td>
<td>19 ± 12</td>
<td>10 ± 8</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Coronary bypass surgery, n</td>
<td>5</td>
<td>2</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>QRS duration, ms</td>
<td>140 ± 25</td>
<td>128 ± 33</td>
<td>95 ± 11</td>
<td>0.03†</td>
</tr>
<tr>
<td>Inducible VT</td>
<td>10</td>
<td>1</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-Blocker, n</td>
<td>9</td>
<td>10</td>
<td>3</td>
<td>0.002</td>
</tr>
<tr>
<td>Amiodarone, n</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>Other antiarrhythmic drugs (Sotalol, Mexilitene)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of patients/group. The following groups were evaluated: heart failure (HF) patients with spontaneous ventricular tachycardia (VT) [HFVT(+) group], HF patients without spontaneous VT [HFVT(−) group], and subjects with structurally normal hearts (HNorm group). *HFVT(+) group vs. HNorm group; †HFVT(+) and HFVT(−) groups vs. the HNorm group.

HNorm patients was maintained during all pharmacological interventions (P = 0.04).

**HRV**

Basal SDRR was <50 ms in both HF groups, but this was not significantly different from the HNorm group (P = 0.26). Atrial pacing abolished HRV in all groups of patients (P < 0.001). There was a trend toward an improvement in SDRR after β-blockade with esmolol (P = 0.08) mainly in the HFVT(+) group. It did not change with isoprenaline infusion (P = 0.63) but was drastically reduced after atropine (P = 0.001) in all three groups.

**QT Responses**

The mean basal uncorrected QT interval was longer in the HFVT(+) group compared with the HFVT(−) group (P = 0.02) and HNorm group (P = 0.004). Compared with the basal state, the mean uncorrected QT interval shortened with atrial pacing in all groups of patients (P < 0.001).

Table 2. *Effect of various interventions on ECG parameters in the three study groups*

<table>
<thead>
<tr>
<th></th>
<th>Mean RR, ms</th>
<th>Atrial Pacing at 80 Beats/min</th>
<th>Atrial Pacing at 100 Beats/min</th>
<th>Esmolol</th>
<th>Isoprenaline</th>
<th>Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (means ± SE)</td>
<td>Atrial Pacing at 80 Beats/min</td>
<td>Atrial Pacing at 100 Beats/min</td>
<td>Esmolol</td>
<td>Isoprenaline</td>
<td>Atropine</td>
</tr>
<tr>
<td>HFVT(+) group</td>
<td>1,001 ± 58§</td>
<td>743 ± 14</td>
<td>&lt;0.001</td>
<td>594 ± 12</td>
<td>1,027 ± 70§</td>
<td>0.091</td>
</tr>
<tr>
<td>HFVT(−) group</td>
<td>891 ± 56</td>
<td>748 ± 14</td>
<td>0.001</td>
<td>600 ± 11</td>
<td>926 ± 69</td>
<td>0.091</td>
</tr>
<tr>
<td>HNorm group</td>
<td>823 ± 59</td>
<td>711 ± 14</td>
<td>0.001</td>
<td>572 ± 11</td>
<td>867 ± 73</td>
<td>0.091</td>
</tr>
<tr>
<td>P value†</td>
<td>0.03</td>
<td>0.21</td>
<td>0.21</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>SDRR, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HFVT(+) group</td>
<td>36 ± 8</td>
<td>4 ± 1</td>
<td>&lt;0.001</td>
<td>3 ± 1</td>
<td>83 ± 17</td>
<td>0.085</td>
</tr>
<tr>
<td>HFVT(−) group</td>
<td>34 ± 8</td>
<td>4 ± 1</td>
<td>&lt;0.001</td>
<td>5 ± 1</td>
<td>42 ± 16</td>
<td>0.085</td>
</tr>
<tr>
<td>HNorm group</td>
<td>51 ± 9</td>
<td>3 ± 1</td>
<td>&lt;0.001</td>
<td>2 ± 1</td>
<td>52 ± 17</td>
<td>0.085</td>
</tr>
<tr>
<td>P value†</td>
<td>0.26</td>
<td>0.25</td>
<td>0.25</td>
<td>0.63</td>
<td>0.63</td>
<td>0.63</td>
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<tr>
<td>Mean QT, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HFVT(+) group</td>
<td>509 ± 21§</td>
<td>441 ± 16§</td>
<td>0.001</td>
<td>425 ± 17§</td>
<td>498 ± 23§</td>
<td>0.45</td>
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<tr>
<td>HFVT(−) group</td>
<td>445 ± 21</td>
<td>437 ± 16§</td>
<td>0.001</td>
<td>423 ± 16§</td>
<td>447 ± 22</td>
<td>0.45</td>
</tr>
<tr>
<td>HNorm group</td>
<td>429 ± 22</td>
<td>398 ± 17</td>
<td>0.001</td>
<td>381 ± 17</td>
<td>414 ± 24</td>
<td>0.45</td>
</tr>
<tr>
<td>P value†</td>
<td>0.009</td>
<td>0.08</td>
<td>0.08</td>
<td>0.02</td>
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<tr>
<td>SDQT, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HFVT(+) group</td>
<td>12 ± 3</td>
<td>11 ± 2§</td>
<td>0.099</td>
<td>11 ± 2§</td>
<td>16 ± 2§</td>
<td>0.47</td>
</tr>
<tr>
<td>HFVT(−) group</td>
<td>13 ± 3</td>
<td>10 ± 1§</td>
<td>0.099</td>
<td>11 ± 2§</td>
<td>15 ± 2</td>
<td>0.47</td>
</tr>
<tr>
<td>HNorm group</td>
<td>7 ± 3</td>
<td>5 ± 1</td>
<td>0.099</td>
<td>7 ± 2</td>
<td>11 ± 2§</td>
<td>0.47</td>
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<tr>
<td>P value†</td>
<td>0.21</td>
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<td>0.008</td>
<td>0.02</td>
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<tr>
<td>SDQT/SDRR</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HFVT(+) group</td>
<td>0.54 ± 0.10</td>
<td>0.33 ± 0.11</td>
<td>0.51</td>
<td>0.37 ± 0.09</td>
<td>0.50</td>
<td>1.03 ± 0.25</td>
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<tr>
<td>HFVT(−) group</td>
<td>0.37 ± 0.10</td>
<td>0.37 ± 0.11</td>
<td>0.38 ± 0.09</td>
<td>1.13 ± 0.24</td>
<td></td>
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<tr>
<td>HNorm group</td>
<td>0.24 ± 0.10</td>
<td>0.29 ± 0.11</td>
<td>0.26 ± 0.10</td>
<td>0.80 ± 0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value†</td>
<td>0.094</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
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</tr>
</tbody>
</table>

SDRR, SD of RR intervals; SDQT, SD of QT intervals. *Intervention effect; †group effect; §compared with HF without VT; ‡compared with normal hearts. *P = 0.02 compared with baseline (linear regression).

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pacing at 80 beats/min ($P = 0.001$) and 100 beats/min ($P < 0.001$) and with isoprenaline ($P = 0.03$) and atropine infusion ($P = 0.02$) in all three groups. The relative baseline differences among HFVT(+) and HFVT(-) and HNorm groups were maintained during all pharmacological interventions ($P = 0.02$).

**QTV**

Group mean values in basal SDQT tended to be higher in HF patients compared with HNorm subjects, but these differences were not significant ($P = 0.21$). Atrial pacing augmented these differences. Both HF groups had significantly higher SDQT than the HNorm group during atrial pacing ($P = 0.008$ and $P = 0.006$ for HFVT(+) vs. HNorm groups and $P = 0.007$ for the HFVT(-) vs. HNorm group). Considered independently, atrial pacing did not reduce QTV in any of the patient groups ($P = 0.1$). Esmolol ($P = 0.47$) and atropine ($P = 0.42$) failed to induce any significant change in SDQT in HF patients; it remained significantly higher than in HNorm subjects ($P = 0.02$). Isoprenaline increased SDQT in the HNorm group ($P = 0.02$) but not in the HF groups (overall main effect of intervention: $P = 0.39$).

**QTV-to-HRV Ratio**

In the basal state, there was a trend toward higher SDQT/SDRR in the HFVT(+) group compared with HFVT(-) and HNorm groups ($P = 0.09$). While esmolol ($P = 0.51$) and isoprenaline ($P = 0.50$) had a neutral effect, SDQT/SDRR increased considerably after atropine infusion ($P = 0.001$), principally due to a reduction in HRV in all three groups.

**DISCUSSION**

**Major Findings**

This study explored mechanisms involved in the generation of electrocardiographic beat-to-beat QTV in HF patients compared with subjects with normal hearts. The main findings from the study are as follows:

1. Beat-to-beat repolarization instability is high in patients with HF, who are prone to recurrent VT.
2. This appears to be at least in part independent of HRV and remains high after uncoupling the effect of HR.
3. Acute therapy with a β-blocker improves HRV but, however, fails to reduce QTV.

**Previous Studies**

Short-term variability in QT intervals is considered a surrogate marker of subtle fluctuations in repolarization duration between consecutive beats (8). The control of sinus node activity via sympathovagal modulation resulting in HRV is well established (32). In contrast, the physiological mechanisms that give rise to or alter QTV are not fully recognized. In healthy hearts, interventions that increase sympathetic tone, such as sudden standing and infusion of isoprenaline, have been shown to increase QTV (55), whereas pharmacological
blockade of β-adrenoceptors reduces QTV (34). Similarly, hypertensive subjects with otherwise normal hearts have been shown to have high QTVs that correlated with their cardiac norepinephrine spillover and systolic blood pressure (9). A recent study (42) in dogs has also shown that QTV is related to left stellate ganglion activity, but only after dogs had developed HF. As sympathetic tone is elevated in HF (29), and QTV is elevated in HF (10), it is appealing to believe that autonomic influences may only override sympathetic influences on QTV in electrically remodeled hearts. The downregulation and desensitization of β₁-adrenoceptors in chronic HF (14, 22) can only partly explain the lack of efficacy of acute β-adrenoceptor blockade on QT as the trend toward HR slowing in HF patients observed after esmolol was comparable with that in HNorm subjects. Nonetheless, high baseline QTV in chronically treated HF patients, as observed in our present study as well as in a previous study (50), suggests that even long-term β-blockade therapy is probably insufficient to reduce high repolarization instability at least in some of these patients.

As observed in a previous study (55), we were able to replicate the increase in QTV with isoprenaline infusion in HNorm subjects. However, this effect was absent in HF groups, strengthening the notion that sympathetic influences may only have limited influence on beat-to-beat repolarization stability in HF (8, 19). As protracted sympathetic stimulation in chronic HF reduces the repolarization reserve (47), the autonomic status presumably ceases to notably affect QTV. Furthermore, in HNorm subjects, we were not able to demonstrate a reduction in QTV from baseline values by β-blockade with esmolol. It is possible that the high repolarization reserve in these patients from functionally normal ion currents raises the threshold for repolarization lability and resists modulation with pharmacological sympathetic blockade. It is also conceivable that QTV, especially during rest, is already at its nadir in normal hearts and that the sympathetic tone is too low for β-blockade to have a significant effect. This is also in line with the observation that...
QT variability (QTV) did not correlate with left stellate ganglion activity in dogs with normal hearts (42). The contrasting results of a previous study (34) where β-blocker with propranolol reduced QTV in individuals with structurally normal hearts are likely due to methodological differences. The effect of propranolol was evaluated during fixed rate atrial pacing, where it may have only abolished the effects of the incidental surge in sympathetic outflow that is associated with cardiac pacing (11).

**Relation with HRV**

The QT interval is intimately linked to HR, reflecting the adaptation of ventricular action potentials to the diastolic interval under physiological conditions (electrical restitution) (56). The QT interval adaptation to HR changes comprises an immediate response to the RR interval change paralleled by a slow, more gradual change that may take several minutes (23). Constant pacing abolishes the effect of physiological HRV on QTV; residual variance in QT despite a lack of HRV likely indicates genuine fluctuations in ventricular activity independent of changes in HR (33). These may be due to a direct autonomic influence, respiration, or underlying ventricular pathology (45). Increased short-term QTV uncoupled from HRV has been shown in ischemic and nonischemic heart disease (10, 26, 35, 40) and was an independent predictor of future VT and SCD in these patients (24, 41, 50). Alongside this strong evidence, a recent study (16) detected changes in RR and QT dynamics during the few hours preceding malignant ventricular arrhythmias.

We demonstrated persistently high QTV in the HFVT(+) group during short-term fixed-rate atrial pacing, suggesting that mechanisms other than HRV may have a dominant role in QT regulation in these patients. Although inconclusive from this study, it is likely that the arrhythmia risk associated with high QTV cannot be evaded with pacing. This observation is in accordance with the results of the Dual Chamber and VVI Implantable Defibrillator trial, where chronic prophylactic atrioventricular pacing at 70 beats/min in ICD recipients without indications for antibradyarrhythmia pacing had no advantage or was even detrimental compared with backup VVI pacing (54). However, these results cannot be extrapolated to biventricular pacing in HF patients. Reverse ventricular remodeling achieved with cardiac resynchronization may improve the dynamics of ventricular repolarization and bring down QTV and thus the arrhythmia risk in these patients (39, 51).

HRV tended to improve in HF patients after acute β-blockade with esmolol and reduced rapidly during vagal blockade by atropine. In comparison, both these drugs had a neutral effect on the high QTV values observed in these patients. This dichotomy in the response of sinus node activity and ventricular repolarization to pharmacological autonomic modulation reinforces the impression of mostly independent physiological mechanisms controlling impulse formation and conduction in HF patients.

**Clinical Significance and Future Directions**

The characteristics of QTV in HFVT(−) patients were more comparable to those of HFVT(+) patients than HNorm subjects. This indirectly demonstrates the progression of spatiotemporal heterogeneity in ventricular repolarization observed as high beat-to-beat QTV in ventricles with cardiomyopathy at high risk for VT. β-Blockers are the mainstay of therapy in patients with systolic dysfunction and have been shown to improve survival in these patients in a large study (21). The antiarrhythmic effect of β-blockers is mainly achieved by suppression of triggers for ventricular arrhythmias and improved HRV and secondarily by improved coronary perfusion and cardiovascular dynamics. This study suggests that β-blockers are ineffective in reducing cardiac repolarization lability, at least in the short term. Nonetheless, this failure to achieve desirable changes in ventricular repolarization cannot be translated to gradual adaptive changes in QTV that may occur slowly with long-term β-blocker therapy and the resultant HF improvement (14, 43). However, the high baseline QTV in HF patients despite chronic treatment with β-blockers suggests that long-term β-blockade may only have a limited effect on QTV. A key implication from this analysis is that since increased QTV is a risk predictor in HF, QTV reduction may in fact be a clinical target for improving life expectancy. However, increased QTV is not altered by acutely varying the autonomic outflow to the myopathic heart. This entails that high QTV perhaps needs its own different set of possible interventions beyond purely neurohumoral management.

**Study Limitations**

While various metrics [e.g., SDQT (27), normalized QTV (24), QTV index (10), short-term variability ratio (37), peak-to-end of T wave interval variability (44)] have been proposed to quantify beat-to-beat repolarization variability, the association of individual measures with future adverse events has been inconsistent among studies (24, 41, 50). Nevertheless, SDQT has been shown to correlate significantly with normalized QTV and the QTV index in HF patients (41). Due to ethical constraints of studying high-risk patient populations with HF, pharmacological interventions could not be performed at higher maximal doses and longer infusion periods in these patients. For similar reasons, the regular β-blocker therapy was not withheld before the planned interventions. The lack of response to esmolol due to an insufficient dosage is possible. Esmolol bolus and high-dose infusion, however, frequently produce hypotension (53), which can smudge the effects on QTV and were suitably avoided. A drug-specific ineffectiveness of esmolol to reduce QTV is unlikely as the efficacy of β-blockers was shown to be a class effect than that of a generic drug (15). Subjects with normal hearts were significantly younger and predominant women compared with the other study groups, which is in accordance with the general demographic profile of patients with supraventricular tachycardia without other cardiovascular diseases (38). However, QTV has been found to be relatively insensitive to age and does not differ between healthy younger and older adults (25, 30). Although sex differences in QTV have been insufficiently investigated, as with the rate corrected QT interval (36), QTV (25) and QTV/HRV (30) have been shown to be higher in women than in men. The higher proportion of women in the HNorm group may therefore have diminished the observed differences in QTV and QTV/HRV between the HNorm and HF groups. Beat-to-beat fluctuations in the QT interval are typically small, and measurement noise might have a considerable impact on QTV measures. In this study, we mostly used lead I, which is characterized by relatively tall T waves and a good
signal-to-noise ratio. Although a larger number of patients could possibly have unequivocally demonstrated the interaction between groups and interventions, we could still reveal clinically relevant observations and trends in HF patients. The sample size was inadequate to demonstrate small differences between HFVT(+) and HFVT(−) patients that may exist. The duration of ECG recording for the assessment of QTV was based on recommendations for short-term HRV analysis (49a). The suitability of this duration for the assessment of short-term QTV has not been systematically investigated. Longer periods of recording may be required to allow a lengthier time for adaptation of the QT interval, which may be a case in HF patients.

Conclusions

Patients with HF and spontaneous VT have larger fluctuations in beat-to-beat QT intervals. This repolarization instability appears to persist despite uncoupling the effect of HR. The effect of acute autonomic nervous system modulation on QTV appears to be limited in HF patients.

ACKNOWLEDGMENTS

Portions of this work have been previously presented at the Annual Scientific Sessions of the Heart Rhythm Society in May 2013 in Denver, CO, and have been previously published in abstract form (Heart Rhythm 10: S388–S433, 2013).

REFERENCES


MODULATION OF QT VARIABILITY IN PATIENTS WITH HEART FAILURE


